

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 31 August 2000 (31.08.00)	
<b>International application No.</b> PCT/US99/25963	<b>Applicant's or agent's file reference</b> 640100-348
<b>International filing date</b> (day/month/year) 04 November 1999 (04.11.99)	<b>Priority date</b> (day/month/year) 13 November 1998 (13.11.98)
<b>Applicant</b> MC INTOSH, Kevin, R. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

09 June 2000 (09.06.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Juan Cruz  Telephone No.: (41-22) 338.83.38
---	---

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 23 JAN 2001

WIPO

PCT

Applicant's or agent's file reference 640100-348	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/25963	International filing date (day/month/year) 04 November 1999 (04.11.1999)	Priority date (day/month/year) 13 NOVEMBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 35/12; A61P 37/06 and US Cl.: 424/93.7; 435/366, 405		
Applicant OSIRIS THERAPEUTICS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 25 August 2000 (25.08.2000)	Date of completion of this report 30 November 2000 (30.11.2000)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Mary B Tung, Ph.D. DELLA MAE COLLINS PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600 Telephone No. 703-308-0111

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.  
PCT/US99/25963

## I. Basis of the report

1. With regard to the **elements** of the international application:\*

- ☒ the international application as originally filed.
- ☒ the description:
  - pages 1-13 \_\_\_\_\_ as originally filed
  - pages NONE \_\_\_\_\_, filed with the demand
  - pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_
- ☒ the claims:
  - pages 14-16 \_\_\_\_\_, as originally filed
  - pages NONE \_\_\_\_\_, as amended (together with any statement) under Article 19
  - pages NONE \_\_\_\_\_, filed with the demand
  - pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_
- ☒ the drawings:
  - pages 1-3 \_\_\_\_\_, as originally filed
  - pages NONE \_\_\_\_\_, filed with the demand
  - pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_
- ☐ the sequence listing part of the description:
  - pages NONE \_\_\_\_\_, as originally filed
  - pages NONE \_\_\_\_\_, filed with the demand
  - pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.  
These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).  
\*\* Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/25963

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. STATEMENT

Novelty (N)	Claims 1-33	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-33</u>	NO
Industrial Applicability (IA)	Claims <u>1-33</u>	YES
	Claims <u>NONE</u>	NO

### 2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 1-33 lack an inventive step under PCT Article 33(3) as being obvious over HAYNESWORTH, et al. (US Patent No. 5,733,542) in view of BRUDER, et al. (US Patent No. 5,536,396) and in further view of DONNELLY, et al. (Exp. Eye Res. 56:157-165, 1993).

The '542 patent teaches a method of administering mesenchymal stem cells (MSCs) to promote autologous or allogeneic engraftment of transplanted tissue (see the abstract, col. 1, lines 17-36 and 50-67 and col. 2, lines 53-63). The '542 patent does not specifically teach fibroblasts. However, the '396 patent teaches that MSCs differentiate into fibroblasts (see Figure 1) and human cells in col. 11. The various times of administration of the fibroblasts, as recited in claims 7-9 is taught by the '542 patent in col. 2, line 67 and bridging over to col. 3, line 6. The '542 and '396 patents do not teach a method whereby the fibroblasts are administered to treat rejection of the transplant by the recipient, as recited in claim 11. However, DONNELLY, et al. teach that fibroblasts produce cytokines which inhibit allogeneic reactions in corneal transplants (see the abstract, in particular). One of ordinary skill in the art would have a reasonable expectation of success in using allogeneic fibroblasts to inhibit an immune response to alloantigens, given the combined teachings of the references. Also one of ordinary skill in the art would recognize that the organs recited in claim 15 are commonly transplanted organs and would have had a motivation to use the methods of the '542 and '396 patents to reduce an immune response against a transplanted tissue, given the teaching by DONNELLY, et al., that fibroblasts produce cytokines that inhibit an immune response against alloantigens. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have arrived at the claimed invention given the combination of reference, absent evidence to the contrary.

#### ----- NEW CITATIONS -----

US 5,733,542A (HAYNESWORTH, et al.) 31 March 1998, see entire document.

US 5,736,396A (BRUDER, et al.) 07 April 1998, see entire document.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.  
PCT/US99/25963

## Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

### Continuation of Certain Documents Cited

#### 1. Certain published documents (Rule 70.10)

Application No

Publication Date

Filing Date

Priority date (valid claim)

Patent No.

(day/month/year)

(day/month/year)

(day/month/year)

None

None

None

None

#### 2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure

Date of non-written disclosure

Date of written disclosure referring to  
non-written disclosure

(day/month/year)

(day/month/year)

None

None

None

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

# INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 99/25963

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K35/12 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40887 A (CHILDRENS MEDICAL CENTER) 19 December 1996 (1996-12-19) page 4, line 5 -page 6, line 2; claims 1-3	1-15,33
X	JOHN J. DONNELLY ET AL: "A soluble product of human corneal fibroblasts inhibits lymphocyte activation. Enhancement by interferon gamma" EXPERIMENTAL EYE RESEARCH, vol. 56, 1993, pages 157-165, XP000876995 page 158, line 1, paragraph 1	1-33
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

23 February 2000

Date of mailing of the international search report

15/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Fernandez y Branas, F

# INTERNATIONAL SEARCH REPORT

Int'l. Patent Application No.

PCT/US 99/25963

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIMABUKURO Y. ET AL: "Interferon-gamma-dependent immunosuppressive effects of human gingival fibroblasts" IMMUNOLOGY, vol. 76, 1992, pages 344-347, XP000876985 cited in the application page 345, column 1-2; figure 1	1-33
A	WO 96 40178 A (RES CORP TECHNOLOGIES INC) 19 December 1996 (1996-12-19) the whole document	1-33



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/25963

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/25963

Patent document: cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640887 A	19-12-1996	US 5741685 A	21-04-1998
		AU 709686 B	02-09-1999
		AU 5980496 A	30-12-1996
		CA 2224226 A	19-12-1996
		EP 0836643 A	22-04-1998
		JP 11506615 T	15-06-1999
WO 9640178 A	19-12-1996	US 5849285 A	15-12-1998
		AU 6105696 A	30-12-1996
		US 5958404 A	28-09-1999